One Year Post Exclusivity Adverse Event Review: Fludarabine

Pediatric Advisory Committee Meeting
September 15, 2004

Susan McCune, MD
Medical Officer
Division of Pediatric Drug Development
Center for Drug Evaluation and Research
Food and Drug Administration

Background Drug Information

- **Moiety:** Fludara® (fludarabine phosphate)
- **Therapeutic Category:** Synthetic adenine nucleoside analog whose cytotoxic action is mediated primarily through inhibition of DNA synthesis
- **Sponsor:** Berlex Laboratories
- **Indication:**
  - **Adults:** Fludarabine is indicated for the treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. The safety and effectiveness of fludarabine in previously untreated or non-refractory patients with CLL have not been established.
  - **Pediatrics:** There are NO approved pediatric indications
- **Original Market Approval:** April 18, 1991
- **Pediatric Exclusivity Granted:** April 3, 2003

FDA Focus on Oncology Drugs for Pediatrics

- Guidance for Industry
  - Pediatric Oncology Studies In Response to a Written Request (June, 2000)
    - Generate new knowledge to assist practitioners
    - Early access to emerging new drugs
  - Approval for pediatric oncology drugs usually based on Phase 2 trials
  - Phase 3 studies usually not requested as a prerequisite for exclusivity
- Best Pharmaceuticals for Children Act
  - Established the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee
  - Prioritize new and emerging therapeutic alternatives available to treat pediatric cancer
- Report to Congress
  - Patient Access to New Therapeutic Agents for Pediatric Cancer (December, 2003)
  - Identified areas in pediatric drug development that could be improved to facilitate access to new agents

Clinical Studies for Exclusivity

- Based on data submitted from two previously published COG trials – CCG-097, and CCG-0895
- CCG-097 was a Phase 1 dose finding and PK study of a loading bolus followed by a continuous infusion of fludarabine in patients with previously treated advanced acute leukemias or solid tumors
  - 9 patients with acute nonlymphocytic leukemia (ANLL)
  - 36 patients with acute lymphocytic leukemia (ALL)
  - 17 patients with solid tumors
- CCG-0895 was a Phase 1/2 dose finding, PK and pharmacodynamic (PD) study of a loading bolus followed by continuous infusion of fludarabine followed by a loading bolus and continuous infusion of Ara-C in children with previously treated advanced acute leukemias

Results of the Clinical Studies for Exclusivity – CCG-097

- Patients with solid tumors maximum tolerated dose (MTD)
  - Loading bolus of 7mg/m^2
  - Continuous infusion of 20 mg/m^2/d for 5 days
  - Dose limiting toxicities were hematologic (myelosupression)
- Patients with acute leukemias MTD not reached
  - Loading bolus of 10.5mg/m^2
  - Continuous infusion of 30.5mg/m^2/d for 5 days
  - Dose limited by concern for potential CNS toxicity seen in adults
  - The goal was marrow ablation so MTD not reached
  - One complete and 3 partial remissions in 26 evaluable children with ALL
- Pediatric adverse events (labeled)
  - Marrow suppression (esp. platelets), fever, chills, asthenia, rash, nausea, vomiting, diarrhea, and infection. No peripheral neuropathy or pulmonary hypersensitivity

Results of the Clinical Studies for Exclusivity – CCG-0895

- Sequential administration of fludarabine (loading bolus of 10.5mg/m^2 with continuous infusion of 30.5mg/m^2/d for 48 hours) followed by Ara-C
- 31 patients
  - 13 patients with ALL
    - 33% complete or partial response
  - 18 patients with acute myeloid leukemia (AML)
    - 50% complete or partial response
- Not able to provide data on the efficacy of fludarabine alone but did provide efficacy and safety data for the combination

New Drug Labeling Resulting from Clinical Trials for Exclusivity (10/03)

CLINICAL PHARMACOLOGY

Special Populations

Pediatric Patients

Limited pharmacokinetic data for FLUDARA FOR INJECTION are available from a published study of children (ages 1-21 years) with refractory acute leukemias or solid tumors (Children's Cancer Group Study 097[1]). When FLUDARA FOR INJECTION was administered as a loading dose over 10 minutes immediately followed by a 5-day continuous infusion, steady-state conditions were reached early.

PRECAUTIONS

Pediatric Use: Data submitted to the FDA was insufficient to establish efficacy in any childhood malignancy. Fludarabine was evaluated in 62 pediatric patients (median age 10, range 1-21) with refractory acute leukemia (45 patients) or solid tumors (17 patients). The fludarabine regimen tested for pediatric acute lymphocytic leukemia (ALL) patients was a loading bolus of 10.5 mg/m^2/day followed by a continuous infusion of 30.5 mg/m^2/day for 5 days. In 12 pediatric patients with solid tumors, dose-limiting myelosuppression was observed with a loading dose of 8 mg/m^2/day followed by a continuous infusion of 23.5 mg/m^2/day for 5 days. The maximum tolerated dose was a loading dose of 7 mg/m^2/day followed by a continuous infusion of 20 mg/m^2/day for 5 days. Treatment toxicity included bone marrow suppression. Platelet counts appeared to be more sensitive to the effects of fludarabine than hemoglobin and white blood cell counts. Other adverse events included fever, chills, asthenia, rash, nausea, vomiting, diarrhea, and infection. There were no reported occurrences of peripheral neuropathy or pulmonary hypersensitivity reaction.

Drug Use Trends in Outpatient Settings (Sales): Fludarabine

- Approximately 280,000 vials of fludarabine were sold in the U.S. annually from May 2001 through April 2004[1].
- Fludarabine was mostly sold to clinics (62%) and non-federal hospitals (30%) during the 12 month post-exclusivity period[1].

[1] IMS Health, IMS National Sales Perspectives™, On-line, May 2001 – Apr 2004, Data Extracted June 2004

Drug Use Trends in Inpatient Settings: Fludarabine

- Nationally projected hospital discharge data from Premier's™ network of approximately 450 acute care hospitals revealed that pediatric use accounted for 3% of discharges between 2002 and 2003[1].
- CHCA™ data demonstrated that from October 2002 through September 2003, there were 95 discharges associated with fludarabine (unchanged from 92 the previous year)[2].
- The principle diagnoses in the pediatric population[1,2]
  - Acute myeloid leukemia without remission
  - Chemotherapy

[1] Premier Perspective™, Jan 2002 - Dec 2003
[2] Child Health Corporation of America™: Pediatric Health Information System (PHIS), Oct 2001 – Sep 2003

Adverse Event Reports: Fludarabine
April 2003 – May 2004

- Total number of reports, all ages:
  - 300 total (113 US)
    - 287 serious (101 US)
    - 125 deaths (33 US)
- Pediatric reports:
  - 10 unduplicated pediatric reports (1 US)
  - Outcomes
    - 3 deaths
    - 7 hospitalized/recovered (1 with sequelae)

Adverse Event Reports: Fludarabine

April 2003 – May 2004

(n=10)

- Recorded medical use
  - 6 preconditioning for bone marrow/stem cell transplant
  - 3 AML relapse
  - 1 Juvenile myelomonocytic leukemia (JMML) with splenectomy
- Age
  - 1 mo - < 2 years = 1
  - 2 - 5 years = 6
  - 6 - 11 years = 1
  - 12 - 16 years = 2

Adverse Event Reports: Fludarabine

April 2003 – May 2004

- Most commonly reported adverse events for all ages in the post-exclusivity period:

Graft vs host disease (40)
Pyrexia (31)
Pancytopenia (23)
Multiorgan failure (18)
Adenovirus infection (15)
Diarrhea (15)
Hepatic failure (15)
Sepsis (14)
Increased bilirubin (13)
Infection (13)
Disease recurrence (12)
Dyspnea (12)
Renal insufficiency (12)
Anemia (11)
Febrile neutropenia (11)
Neutropenia (11)
Pneumonia (11)
Thrombocytopenia (11)
Abdominal pain (10)
Drug ineffective (10)
Drug toxicity (10)
Malignant neoplasm progression (10)
Platelet count decreased (10)
Vomiting (10)

Underlined = Unlabeled event

Adverse Event Reports: Fludarabine

April 2003 – May 2004

Deaths (n=3)

- 4 year old with ALL received fludarabine for preconditioning for stem cell transplant. The day after transplant, she developed fever, shock and multiorgan failure. Other medications were Thiotepa and ATG. (Non-US)
- 8 year old with ALL received irradiation, fludarabine and cyclosporine followed by stem cell transplant. He became febrile 6 days later with rash, generalized edema, tachycardia, abdominal pain and cardiac arrest. (Non-US)
- 13 year old with bone sarcoma of the rib received fludarabine as preconditioning for stem cell transplant. She developed "carcinomatous pleurisy" and died of disease progression. She had also received busulfan. (Non-US)

Adverse Event Reports: Fludarabine
April 2003 – May 2004
Hospitalizations (n=7)

- 18 month old with hepatic veno-occlusive disease with bone marrow transplant (BMT) for beta-thalassemia treated with rtPA with complete resolution. Additional medications were cyclophosphamide and busulfan. (Non-US)
- 2 year old with relapsed AML developed photophobia on the FLAG (fludarabine, cytarabine, and granulocyte colony stimulating factor) study (resolved). No photophobia on rechallenge. (Non-US)
- **3 year old with relapsed AML on FLAG study developed bilateral blindness which resolved leaving some degree of blindness. Additional medication was ambisome. (Non-US)**
- 4 year old with AML relapse who developed encephalopathy and recovered. Numerous concomitant medications. (Non-US)

Adverse Event Reports: Fludarabine

April 2003 – May 2004

Hospitalizations (n=7) (cont.)

- 4 year old with JMML with splenectomy in preparation for BMT. One day after surgery developed fever and pneumonia requiring intubation. Also has a history of neurofibromatosis. Additional medications included cis-retinoic acid and Ara-C. (US)
- 5 year old with AML with BMT who developed aphasia, "vigilance disturbance" and non-specific encephalopathy 30 days after transplant. Additional medications included ATG, solumedrol, thioguanine, amsacrine, thiotepa, and cyclosporine. (Non-US)
- **13 year old with BMT for aplastic anemia who developed cardiac tamponade and cardiac failure 4 days after transplant. She was treated with diuretics and pressors and recovered after 4 days. Additional medications included methotrexate, tacrolimus, cyclophosphamide and ATG. (Non-US)**

Adverse Event Reports: Fludarabine

April 2003 – May 2004

Clinically Significant Pediatric Adverse Events

- **Cardiac failure (2)/Cardiac tamponade (1)/Cardiac arrest (2)**
  - Labeled for edema and pericardial effusion in adults
- **Abdominal Pain (2)**
  - Labeled for nausea/vomiting, anorexia, diarrhea, stomatitis and GI bleeding in adults
- **Blindness/Optic nerve disorder (2)**
  - Labeled for visual disturbance and blindness in adults
- **Encephalopathy (2)/MRI abnormal (2)**
  - Labeled for weakness, agitation, confusion and coma in adults

Fludarabine Boxed Warning

Fludara®
(fludarabine phosphate)

FOR INJECTION
FOR INTRAVENOUS USE ONLY

Rx only

WARNING: FLUDARA FOR INJECTION should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. FLUDARA FOR INJECTION can *severely* suppress bone marrow function. When used at high doses in dose-ranging studies in patients with acute leukemia, FLUDARA FOR INJECTION was associated with severe neurologic effects, including blindness, coma, and death. This severe central nervous system toxicity occurred in 36% of patients treated with doses approximately four times greater (96 mg/m^2/day for 5-7 days) than the recommended dose. Similar severe central nervous system toxicity has been rarely (≤0.2%) reported in patients treated at doses in the range of the dose recommended for chronic lymphocytic leukemia.

Instances of life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported to occur after one or more cycles of treatment with FLUDARA FOR INJECTION. Patients undergoing treatment with FLUDARA FOR INJECTION should be evaluated and closely monitored for hemolysis.

In a clinical investigation using FLUDARA FOR INJECTION in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL), there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of FLUDARA FOR INJECTION in combination with pentostatin is not recommended.

Summary

- Labeled and unlabeled adverse events have been reported.
- There are a number of pediatric adverse events that were reported in the post-exclusivity period that were not recognized in the clinical trials done for exclusivity.
- These adverse events have been labeled for adults.
- These serious adverse events include encephalopathy, blindness (and other visual disturbances), and cardiac tamponade/failure.
- These patients tend to be on complicated pretransplant regimens that involve multiple medications and immunosuppression.
- This completes the one-year post-exclusivity adverse event monitoring as mandated by BPCA.
- FDA will continue its routine monitoring of adverse events for this drug.